www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2019; 8(6): 638-641

www.thepharmajournal.com
Received: 28-04-2019
Accepted: 30-05-2019

GV Osyodlo
Ukrainian Military-Medical Academy, Kyiv city, Ukraine

SA Bychkova
Ukrainian Military-Medical Academy, Kyiv city, Ukraine

Correspondence
GV Osyodlo
Ukrainian Military-Medical Academy, Kyiv city, Ukraine

Bronchopulmonary «Masks» of Gastroesophageal reflux disease

GV Osyodlo and SA Bychkova

Abstract
The objective of the work is to determine the leading extraesophageal symptoms, disturbance of spirometric indices and changes in the immune system in patients with GERD and in case of comorbid course with COPD.
98 male patients were examined, who were divided into three groups. 1 group (34 patients) consisted of GERD patients, who had extraesophageal bronchopulmonary manifestations; 2 group consisted of 32 patients with first time COPD; and 3 group consisted of 32 patients with the combination of COPD and GERD.
It was determined, that GERD is a multiple-symptom disease, which is characterized by extraesophageal manifestations. Bronchopulmonary manifestations of GERD are a cough syndrome characterized by the presence of a non-intensive, unproductive cough with a small amount of mucous sputum and is combined, in most cases, with the hoarseness of the voice. Cough syndrome during GERD is characterized by a lack of obstructive changes in the study of indicators of external respiration and elevated levels of proinflammatory cytokines in the blood serum. The combined course of GERD and COPD is characterized by the development of intense cough with expectoration, combined with obstructive changes in the indicators of the external respiration, and is characterized by more active proinflammatory changes in the immune system with elevated serum levels such as TNF-α, IL1-β and IFNγ.

Keywords: Bronchopulmonary, Gastroesophageal

Introduction
Lately, the issue of gastroesophageal reflux disease (GERD) attracts attention due to the considerable prevalence of this disease. The worldwide organization of gastroenterologists has recognized GERD as a leading disease in the 21st century, which afflicts 20 to 50 % of the population of different countries, which also causes a decrease in the quality of life, work capacity and the development of a number of complications, such as Barrett's esophagus. Over the past 20 years, GERD has occupied one of the prominent places among diseases of the digestive system, to which scientists around the world pay close attention with the aim of further study of etiology, pathogenesis, prognosis of the course and effective treatment. Much attention has recently been given to the study of comorbid pathology, namely the combined course of GERD and other diseases such as functional dyspepsia, irritable bowel syndrome, pancreatitis, coronary heart disease and heart rhythm disorders, obesity, chronic obstructive pulmonary disease (COPD), bronchial asthma (BA), hypertonic disease, etc. [1].
It should be noted that when combined with another somatic pathology, the GERD acquires certain features, complaints that are not always inherent in the pathology of the gastrointestinal tract are coming to the fore. One of the manifestations of an atypical course of GERD may be the cough syndrome, which becomes a main complaint of the patient. According to the literature, among patients of all age groups who do not smoke, do not take ACE-inhibitors, have no changes in the lungs in the X-ray examination of the chest organs, chronic cough develops in 93,6% of cases with three underlying diseases [2]: postnasal drip syndrome (PDS), obstructive pulmonary disease (bronchial asthma and chronic obstructive pulmonary disease), and GERD.
The basis of the PDS is the presence of a secretion that flows into the throat part of the throat, mechanically stimulates the afferent part of the arc of the cough reflex, causing the appearance of cough. The verification of this diagnosis is based on anamnesis data (when the patient describes the characteristic feeling of secretion at the back of the pharynx), objective examination data and laboratory test results.

COPD is almost always manifested by productive cough, but very rarely occurs at an early stage, when the only manifestation is this very symptom [3]. BA (cough version) is one of the most common causes of chronic cough.

The third most frequent cause is the GERD; the mechanism of cough development consists of a vagus-mediated esophageal and tracheobronchial reflex. In 2/3 of patients with this condition, other gastrointestinal symptoms may not be present, although they may complain of heartburn (epigastric burning) after a meal. Increased acidity in the lower esophagus is a prerequisite for the appearance of chronic cough [1]. In this case, it is important to evaluate the duration, frequency of episodes of reflux, and also to establish a correlation with episodes of cough.

The objective of the work is to determine the leading extraesophageal symptoms, disturbance of spirometric indices and changes in the immune system in patients with GERD and in case of comorbid course with COPD.

Material and methods

In order to solve the presented objective 98 male patients were examined, who were divided into three groups. 1 group (34 patients) consisted of GERD patients, who had extraesophageal bronchopulmonary manifestations; 2 group consisted of 32 patients with first time COPD; and 3 group consisted of 32 patients with the combination of COPD and GERD.

Average age of the patients constituted (47,6±3,4) years; all patients were on examination and hospitalised in the clinics of National Military-Medical Clinical Centre «Main Military Clinical Hospital» of the Ministry of Health of Ukraine.

The GERD diagnosis was established pursuant to the Unified clinical protocol of primary, secondary (specialised) medical care "Gastroesophageal reflux disease" (Order of MH of Ukraine No. 943), 2013 [4]. The criteria of diagnosing GERD were the following: the appearance of symptoms that disturb the patient and/or the development of complications arising from the reflux of the stomach contents, namely, heartburn and regurgitation (eructation, acid eructation) occurring at least once a week, and the most common complication – reflux esophagitis. When establishing a clinical diagnosis, the extent of damage to the esophagus was determined after an endoscopic examination (A, B, C, D) according to the Los Angeles Classification (1994). To verify the type of reflux (acid or alkaline) and to determine the symptom index, the patient undergoes a many-hour pH-impedansometry (Acydograph ААГЩ 941. 114. 001 ІЕ).

The assessment of clinical symptoms of bronchopulmonary system damage was conducted with the help of rating scale of I. V. Suvorkina (2005) [5]:

- cough: 0 - none, 1 - mild (slight coughing in the morning), 2 - moderate (coughing in the morning and during the day), 3 – severe;
- sputum amount: 0 – none, 1 – to 5 ml/day, 2 – to 15 ml/day, 3 – to 30 ml/day, 4 – more than 30 ml/day.

The COPD diagnosis was established pursuant to the Order of MH of Ukraine [6]. All COPD patients underwent the course of the disease assessment test (COPD Assessment Test, CAT) [6]. The assessment of dyspnea intensity was conducted by the modified dyspnea scale - Medical Research Council Dyspnea Scale (mMRC), according to which:

0 points – dyspnea only with very intense exercise;
1 – dyspnea at fast pace, slight uphill;
2 – dyspnea forces to go slower than people of the same age;
3 – dyspnea requires stopping during the walk every 100 m;
4 – dyspnea does not allow going outside the home or appears when changing clothes.

Spirography was performed on the «Spirosift SP-5000» (Fucuda Denshi, Japan).

The levels of pro- and anti-inflammatory cytokines, IL-17A, interferon-γ (IFN-γ), and the content of soluble sICAM-1 sVCAM adhesion molecules were determined using Ukraine-certified enzyme multiplied immunoassay kits based on Pro Con (Russia) and Diaclon (France) companies' methodology, a transforming growth factor-β (TGF-β) - «Genzyme diagnostics». The content of subpopulations of lymphocytes with the CD54+, CD11b+ and CD62L+ phenotypes was determined by indirect immunofluorescence using monoclonal antibodies.

Statistical data was processed using the Microsoft XP Excel application program package, as well as the standard version of the Statistical Package for the Social Sciences (SPSS) 17.0.

Results and Discussion

Table 1 shows basic clinical, demographic characteristics of the patients, and states the main complaints of all three groups of patients.

Table 1: Clinical characteristics of examined patients (M±m)

Clinical features	1-st group (n=34)	2-nd group (n=32)	3-nd group (n=32)	p*
Average age, years	46,3±3,2	48,9±2,8	47,7±3,9	p>0,1
Body mass index, kg/m^2	25,5±1,5	30,3±1,8	26,8±2,8	p_{1-2}<0,05 d_{2-3}<0,05
Smocking, n (%)	19 (55,88%)	32 (100%)	32 (100%)	
Smocking index, pack/years	19,4±2,5	26,8±4,9	24,7±1,9	p_{1-2}<0,05 p_{1-3}<0,05
Epigastric burning sensation, n (%)	33 (97,05%)	-	28 (87,50%)	
Regurgitation sensation, n (%)	30 (88,23%)	-	26 (81,25%)	
Sour regurgitation sensation, n (%)	26 (76,47%)	-	15 (46,88%)	
Acute disease start (acute attack), n (%)	19 (55,88%)	2 (6,25%)	4 (12,50%)	
Cough, points	1,3±0,1	2,8±0,2	3,1±0,2	p_{1-2}<0,05 p_{1-3}<0,05
Sputum, points	1,1±0,1	3,2±0,3	3,4±0,2	p_{1-2}<0,05 p_{1-3}<0,05
Sputum's nature:				
mucus, n (%)	18 (52,94%)	23 (71,87%)	17 (53,13%)	
mucus-pus, n (%)	-	9 (28,12%)	13 (40,63%)	
pus, n (%)	-	-	2 (6,25%)	
Voice hoarseness, n (%)	27 (79,41%)	-	14 (43,75%)	
mMRC, points	-	1,1±0,1	1,4±0,1	p>0,1
CAT, points	-	7,5±0,8	8,2±0,3	p>0,1
Harsh respiration, n,%	-	29 (90,63%)	31 (96,88%)	
Scattered dry rales, n,%	-	22 (68,75%)	30 (93,75%)	

Note: p – probability of indicators' difference

As can be seen from the data presented in Table 1, patients of 2 group showed a significant increase in body mass index (BMI) compared with patients in groups 1 and 3. Particular attention is paid to the fact that all patients in groups 2 and 3 were smokers or former smokers with a high smoking index. 55.88% of patients in group 1 were also smokers, indicating that this habit is a provocative factor in the development not only of the pathology of the respiratory organs, but also of the gastrointestinal tract. The main complaint in all groups of patients was cough, but its intensity was significantly higher in patients with COPD (patients in groups 2 and 3). In patients from groups 2 and 3, intense coughing was accompanied by expectoration in daily amount of 30 and more ml, which usually excreted in the morning with intense cough. The type of sputum in patients of groups 2 and 3 was predominantly mucous.

It should be noted that in the group of patients with GERD, one of the main complaints was also cough, but its intensity was lower in probability compared to other groups of patients. The cough was accompanied by the excretion of a small amount of sputum of the mucous nature. 27 patients (79.4%) were found to have hoarse voices.

Thus, in the initial examination, all patients appealed for medical assistance for cough syndrome; its intensity, the presence or absence of sputum could not always indicate a lesion of the bronchopulmonary system. As a separate diagnostic criterion can serve only the acute beginning of the development of cough syndrome, which is more common in patients with GERD (55.9% of patients), while in patients with COPD with the phenotype of chronic bronchitis, the cough developed gradually, and its intensity increased over time.

In addition to cough with expectoration, in patients of groups 1 and 3 were noticed complaints of heartburn, sensation of regurgitation including with acid content.

Physical signs of the lesion of the bronchopulmonary system (harsh breath, scattered dry rales) were detected in patients with COPD or in patients with a combined pathology.

In the initial examination of all patients, the study of indicators of the external respiration function (ERF) was conducted to confirm or exclude obstructive diseases of the respiratory organs.

The analysis of the indicators presented in Table 2 showed that in the group of patients with GERD (group 1), all indicators were preserved, no obstructive or restrictive changes were detected.

Table 2: Spirometric indecis of examined patients (M±m)

Indicators	1-st group (n=34)	2-nd group (n=32)	3-nd group (n=32)	p*
FEV 1, %	86,1±3,2	76,9±2,8	75,5±3,1	$p_{1-2}<0,05$ $p_{1-3}<0,05$
FVC, %	83,7±2,1	77,5±3,3	76,9±3,1	$p_{1-2}<0,05$ $p_{1-3}<0,05$
FEV1/FVC	88,2±3,4	65,3±2,6	63,1±2,8	$p_{1-2}<0,05$ $p_{1-3}<0,05$
PEF	82,5±3,6	72,2±3,8	73,5±2,9	$p_{1-2}<0,05$ $p_{1-3}<0,05$
MEF 25-75%	82,8±2,1	71,4±3,3	72,6±2,7	$p_{1-2}<0,05$ $p_{1-3}<0,05$
VC, %	93,5±4,8	94,8±4,6	94,5±4,3	P>0,1
FEV1 gain %	3,6±0,8	4,7±1,1	3,9±0,7	P>0,1

Note: p – probability of indicators' difference

In the 2nd and 3rd groups of patients diagnosed with «first time diagnosed COPD, Group A», were found obstructive disorders that were manifested by a probable decrease in FEV 1, Forced vital lung capacity (FVC), MEF from 25-75% with a level of obstruction corresponding to GOLD 1, in a small number of patients – 7 people – GOLD 2. In addition, the ratio of FEV1 / FVC less than 0.7, which is one of the diagnostic criteria for COPD, was noted in these patients, the obstruction was evaluated as irreversible during the bronchodilation test (gain of FEV1 was 4.7±1.1% in group 2 and 3.9±0.7% - in group 3).

An immunological examination was conducted for all groups of patients, which included the determination of serum concentration of pro- and anti-inflammatory cytokines, the level of soluble adhesion molecules, as well as the expression of activation adhesive molecules on peripheral blood lymphocytes in the examined patients.

It is known from the literature that there is an imbalance in T-cell subpopulation in patients with GERD, which plays a key role in modulating the functions of immunocompetent cells, and plays a significant role in the relapse of the disease and promotes changes in the cellular structure of the esophagus mucosa with the formation of intestinal metaplasia, in areas with which there is a decrease in apoptosis, proliferation processes are activated, and the activity of glutathione-S-transferase decreases, which, in turn, leads to a decrease in the protection of the cells of the esophagus mucosa from free oxygen radicals and the formation of erosive lesions [7].

Table 3: Immunological characteristics of examined patients (M±m)

Indicators	1-st group (n=34)	2-nd group (n=32)	3-nd group (n=32)	p*
$CD54^+$lymphocytes,%	12,6±0,8	18,2±0,5	17,7±0,6	$p_{1-2}<0,05$ $p_{1-3}<0,05$
$CD11b^+$lymphocytes,%	21,5±1,4	33,2±1,6	32,7±1,3	$p_{1-2}<0,05$ $p_{1-3}<0,05$
$CD62L^+$lymphocytes,%	28,3±1,2	40,9±1,6	41,6±1,3	$p_{1-2}<0,05$ $p_{1-3}<0,05$
TNF-α, pg/ml	113,6±4,2	82,7±3,9	115,3±4,9	$p_{1-2}<0,05$ $p_{2-3}<0,05$
IL-1β, pg/ml	106,8±5,2	79,42±3,6	112,6±5,8	$p_{1-2}<0,05$ $p_{2-3}<0,05$
IL-6, pg/ml	14,3±0,6	23,9±1,2	21,3±1,3	$p_{1-2}<0,05$ $p_{1-3}<0,05$
IFN-γ, pg/ml	48,6±2,9	83,9±2,3	86,4±2,6	$p_{1-2}<0,05$ $p_{1-3}<0,05$
IL-4, pg/ml	20,1±0,9	19,7±0,8	22,4±3,3	p>0,1
TGF-β, pg/ml	39,4±4,1	62,3±3,4	65,8±4,1	$p_{1-2}<0,05$ $p_{1-3}<0,05$
IL-17A, pg/ml	17,3±2,7	20,3±1,1	21,1±2,6	$p_{1-2}<0,05$ $p_{1-3}<0,05$
sVCAM, pg/ml	18,6±1,2	22,3±1,6	21,1±1,9	p>0,1
sICAM-1, ng/ml	175,5±11,3	228,3±15,4	230,9±12,7	$p_{1-3}<0,05$

Note: p – probability of indicators' difference

Patients with GERD showed a significantly higher level of proinflammatory cytokines in serum, namely, TNF-α and IL-1β, against the background of the preserved level of anti-inflammatory IL-4, as well as TGF-β and IL-17. In addition, in this group of patients,was noted the normal content of serum soluble sVCAM and sICAM-1 adhesion molecules and the expression of activation adhesive molecules on lymphocytes, which is directly related to the activation processes of the immune system cells (CD4+lymphocytes) in response to irritation of mucous membrane of the gastrointestinal tract with hyperproduction of proinflammatory cytokines. Patients in group 2 (isolated COPD) have been noticed to activate the T-helper cells type 1 of the immune system with a significant prevalence of IFN-γ in blood serum as opposed to other proinflammatory cytokines. At the same time, an increase in TGF-β serum concentration was found, which is an immunological feature of bronchial remodelling and the formation of irreversible bronchial obstruction [8]. In addition, an individual analysis of the IL-17A serum concentration found that patients with GOLD 2 level of obstruction (7 persons) had a significantly higher IL-17A level compared to the mean in the group. During an immunological examination, in patients with COPD, high serum concentration of soluble adhesion molecules and high expression of adhesive markers on activated lymphocytes were also detected. In case of comorbid course of GERD and COPD, in the immune system of patients, were detected both manifestations of classical activation of the immune system with hyperproduction of proinflammatory cytokines, and simultaneous activation of type 1 T-helper cells with hyperproduction of IFN-γ. Consequently, the inflammatory process of higher intensity with higher levels of proinflammatory cytokines leads to a stronger activation of immunocompetent cells and the synthesis of adhesive molecules by them. The high serum concentration of the soluble sICAM-1 adhesion molecule, in addition, combined with increased levels of ICAM-1 receptor expression in peripheral blood lymphocytes, CD54+ lymphocyte contents significantly exceeded the indicators of healthy subjects in both groups of patients, by 78.86% and 64.4 % respectively. In addition, an increased percentage of CD62L+ lymphocytes was detected in both groups of patients, respectively, by 50.53% and 44.52%, because it is CD62L (L-selectin) that ensures attachment of lymphocytes to the endothelial wall.

Conclusions

1. GERD is a multiple-symptom disease, which is characterized by extraesophageal manifestations. Bronchopulmonary manifestations of GERD are a cough syndrome characterized by the presence of a non-intensive, unproductive cough with a small amount of mucous sputum and is combined, in most cases, with the hoarseness of the voice.
2. Cough syndrome during GERD is characterized by a lack of obstructive changes in the study of indicators of external respiration and elevated levels of proinflammatory cytokines in the blood serum.
3. The combined course of GERD and COPD is characterized by the development of intense cough with expectoration, combined with obstructive changes in the indicators of the external respiration, and is characterized by more active proinflammatory changes in the immune system with elevated serum levels such as TNF-α, IL1-β and IFNγ.

References

1. Osyodlo GV, Radushynska MV, Huryanov VH. Complex therapy of gastroesophageal reflux disease in combination with anxious-depressive states of the participants of antiterroristic operation. Gastroenterology. 2018; 52:14-20.
2. Unified clinical protocol of primary medical care "Cough in adults". Order of MH of Ukraine dated June 8, 2015 No. 327. Clinical immunology, allergology, infectology. 2016; 3:38-45.
3. Khimion LV, Yashchenko OB. Effective and safe treatment of dry cough – topical problem of general medical practice. Family medicine. 2015; 1:130-133.
4. Unified clinical protocol of primary (secondary) specialised medical care "Gastroesophageal reflux disease". Order of Ministry of Health of Ukraine dated, 2013 No. 943// http://www.moz.gov.ua/ua/portal/dn_20131031_0943.html
5. Suvorkina IV. Efficiency of using fenspiride (erespal) in the treatment of patients with chronic obstructive pulmonary disease of severe course. Ukrainian pulmonological magazine. 2005; 3:28-31.
6. Order No.555 of MH of Ukraine dated 27.06.2013. On approval and implementation of medico-technological documents on standardisation of medical care for chronic obstructive lung disease. http://www.moz.gov.ua/ua/portal/dn_20130627_0555.html
7. Isomoto H, Inoue K, Kohno S. Interleukin-8 levels in esophageal mucosa and long-term clinical outcome of patients with reflux esophagitis. Scandinavian Journal of Gastroenterology. 2007; 42:410-411.
8. Bychkova S. Role of interleukin-17 in disease course of different phenotypes of chronic obstructive pulmonary disease. Pharma Innovation Journal. 2017; 6(8):264-267.